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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,360	01/05/2005	Julie Kay Bush	X-14884	5540

25885 7590 01/28/2010

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ART UNIT	**PAPER NUMBER**
1612	

NOTIFICATION DATE	DELIVERY MODE
01/28/2010	ELECTRONIC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JULIE KAY BUSH, MARGARET MARY FAUL, and
SUSAN MARIE REUTZEL-EDENS

Appeal 2009-010640[1]
Application 10/520,360
Technology Center 1600

Decided: January 27, 2010

Before ERIC GRIMES, FRANCISCO C. PRATS, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to a crystalline mono-hydrochloride salt of a compound that inhibits protein kinase C. The Examiner rejected the claims as obvious.

We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

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[1] Eli Lilly and Company is the real party in interest.

STATEMENT OF THE CASE

Claims 2 and 15 are pending and on appeal (App. Br. 2), and read as follows:

> Claim 2 Crystalline 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole mono-hydrochloride having an X-ray diffraction pattern which comprises the following peaks: 6.8 ± 0.1, 10.9 ± 0.1, 14.2 ± 0.1 and 16.6 ± 0.1° in 2θ; when the pattern is obtained from a copper radiation source (CuKα; λ = 1.54056 Å).
>
> Claim 15 A pharmaceutical composition comprising a salt of claim 2 and a pharmaceutical carrier.

Two obviousness rejections are before us for review:[2]

(1) Claims 2 and 15, rejected under 35 U.S.C. § 103(a) as obvious in view of Teicher[3] (Ans. 4-5); and

(2) Claims 2 and 15, rejected under 35 U.S.C. § 103(a) as obvious in view of Heath[4] (Ans. 5).

OBVIOUSNESS

ISSUE

The Examiner finds that, in addition to disclosing the free base form of the claimed compound, Teicher teaches that the compound can exist as pharmaceutically acceptable acid addition salts, including, preferably, the hydrochloric acid and mesylate salts (Ans. 4). The Examiner also finds that Teicher teaches preparing crystalline forms of the compound, as evidenced by the disclosure of solvates that result from crystallization (*id.*).

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[2] The Examiner withdrew the appealed anticipation rejections (Ans. 3).
[3] Teicher et al., WO 02/02094 A2, published January 10, 2002.
[4] Heath, Jr. et al., U.S. Patent No. 5,545,636, issued August 13, 1996.

The Examiner concedes, however, that Teicher differs from the claims by specifically teaching the di-hydrochloride salt, rather than the claimed mono-hydrochloride (*id.*). The Examiner nonetheless concludes that an ordinary artisan would have considered the claimed crystalline mono-hydrochloride salt obvious because Teicher teaches the "crystalline forms of dihydrochloride and teaches that since it contains a basic moiety, it can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric acid (lines 13-32, page 8), so the monochloride [sic] salt would be fairly suggested thereby" (Ans. 5).

In the second obviousness rejection the Examiner finds that Heath, like Teicher, discloses that the claimed compound is useful when prepared in the hydrochloride salt form (*id.*). The Examiner reasons, therefore, that a person of ordinary skill in the art would have been "motivated to prepare the crystalline acid addition . . . pharmaceutically acceptable salts such as hydrochloride salts because HEATH et al teaches the crystalline forms of this compound. The pharmaceutical composition will be the same as the prior art because the compound is the same as presented" (*id.*).

Appellants' arguments are similar for both rejections. Appellants contend, among other things, that the references do not "teach or suggest the specific crystalline mono-hydrochloride salt . . . claimed by Appellants having the specific XRD [x-ray diffraction] pattern claimed by Appellants, much less how to make it" (App. Br. 12, 14).

Moreover, Appellants urge that Examiner has not presented any rationale explaining "how one of ordinary skill would predict and prepare the particular crystalline form of the mono-hydrochloride salt of the

compound [claimed] by Appellants as is required" for a conclusion of obviousness (*id.* at 12-13 (citing *In re Cofer*, 354 F.2d 664, 668 (CCPA 1966); *In re Hoeksema,* 399 F.2d 269, 274 (CCPA 1968)).

Rather, Appellants argue:

> [T]he Examiner fails to take into account the unpredictability of the crystallization art, such that the structure of any allegedly obvious new form, or its associated properties, cannot be determined by theory. Acid-base reactions (i.e., to form acid addition salts) are predictable in solution based on the relative pKas of the reactants. However, the resulting salts are generally amorphous, and there is no reliable predictor of crystallization.

(App. Br. 13.)

In view of the positions advanced by Appellants and the Examiner, the issue with respect to these rejections, therefore, is whether the Examiner erred in concluding that the specific form of the compound recited in the claims would have been obvious to one of ordinary skill in the art, in view of the teachings of either Teicher or Heath.

FINDINGS OF FACT ("FF")

The Claims

1. Claim 2 recites crystalline 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole mono-hydrochloride. Claim 2 requires the crystalline salt to have an X-ray diffraction pattern "which comprises the following peaks: 6.8 ± 0.1, 10.9 ± 0.1, 14.2 ± 0.1 and 16.6 ± 0.1° in 2θ; when the pattern is obtained from a copper radiation source (CuKα; λ = 1.54056 Å)."

2. The Specification discloses that, with respect to the free base form of the claimed compound ("FB"), "unpredictable formation of solvates complicated the commercial synthesis to such an extent that it became necessary to develop an alternative form for large-scale commercialization" (Spec. 2).

3. The Specification discloses that, to avoid the difficulties in large scale synthesis of the free base form of the compound, prior art therapeutic methods used the dihydrochloride salt of the compound ("FB-2HCl") (*id.*).

The Specification discloses, however, that "FB-2HCl is hygroscopic. In addition, although FB-2HCl appears to be crystalline by optical light microscopy, more detailed study by X-ray powder diffraction (XRD) has revealed that this material is in fact only poorly crystalline" (*id.*).

4. The Specification discloses that, "[s]urprisingly, in accordance with the invention, it has now been discovered that the monohydrochloride salt of FB [("FB-HCl")] is capable of being reproducibly produced on a commercial scale, is not significantly hygroscopic, is sufficiently stable for use in oral formulations, and can be produced in a highly crystalline state" (*id.*).

5. The Specification discloses that "FB-HCl, prepared via addition of 1 equivalent of concentrated or 1N hydrochloric acid to a mixture of FB in a lower alcohol, *e.g.*, methanol, isopropanol or 2-butanol, or in a mixture of a lower alcohol and water, is crystalline" (*id.* at 5).

6. The Specification also discloses that when an aqueous solution of 40 mg/ml or more of the dihydrochloride salt of the compound is prepared at room temperature, crystals of the monohydrochloride salt precipitate from the solution (*id.*).

7. Appellants' Example 1 discloses the specific process used to prepare the monohydrate crystal having the X-ray diffraction pattern recited in claim 2:

> To a 3 necked flask equipped with heating mantle, condenser and distillate take off add FB (59.0g, 114.4 mols), 2-butanol (949 ml, 16.1 vols), deionized water (621.4 mL, 10.5 vols) and HCl (food grade: 12.24 mL, 14.13 g, 0.21 volumes, 1.05 equivalents). Heat the reaction to reflux and remove half of the solvent by distillation. Slowly add 2-butanol (27 volumes) over 2 hours, while maintaining a constant solvent level in the reaction flask. Cool the reaction to room temperature over 60 minutes, then cool to 0-5 °C and stir for 1-2 hours. Filter the product and wash the filter cake with 2 volumes of 2- butanol and dry the filter cake overnight at 50°C under vacuum.

(*Id.* at 14.)

Teicher

8. Teicher discloses "a method for treating a neoplasm which comprises administering to a mammal in need thereof, an anti-neoplastic agent or therapeutic radiation in combination with . . . the compound of Formula I . . . or a pharmaceutically acceptable salt or solvate thereof" (Teicher 6-7).

It is undisputed that the compound of Teicher's Formula I is the compound recited in the appealed claims.

9. Teicher discloses that "[b]ecause it contains a basic moiety, the compound of Formula I can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric . . . . Particularly the hydrochloric and mesylate salts are used" (*id.* at 8).

10. Teicher discloses:

> The pharmaceutically acceptable salts of the compound of Formula I can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

(*Id.* at 9.)

11. Teicher's examples disclose using the compound of Formula I, by itself or in combination with other agents, to treat tumors (*id.* at 12-19). Teicher discloses that, in each of the examples, "the compound of Formula I is administered as the dihydrochloride salt, and the amounts administered are given in terms amounts of the dihydrochoride [sic] salt" (*id.* at 11).

Heath

12. Heath discloses "isozyme selective [protein kinase C] inhibitors, of the Formulas II, III, and IV" (Heath, col. 3, ll. 38-39).

Among the compounds encompassed by those formulae is the compound prepared in Example 49 (*id.* at cols. 45 and 46), which is undisputed as being the claimed compound.

13. Heath discloses that, "[b]ecause of the basic moiety, the compounds of Formulas II, III, or IV can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric . . . " (*id.* at col. 10, ll. 37-40).

14. Heath also discloses:

> The pharmaceutically acceptable salts of compounds of Formulas II, III, or IV can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can also be

> prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent. Such solvates are within the scope of the present invention.

(*Id.* at col. 10, l. 64, through col. 11, l. 4.)

PRINCIPLES OF LAW

In *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007), the court concluded that a claim to the besylate salt of the hypertension-treating compound amlodipine was obvious. The court based its conclusion on the prior art's generic teaching of the usefulness of the compound in the salt form, and evidence showing that there were only a limited number of pharmaceutical salts available that could be combined with the compound, the besylate salt being disclosed as advantageous in certain pharmaceutical formulations. *Id.* at 1362-1364.

In the context of preparing alternative forms of prior art compounds, however, the court in *In re Cofer*, 354 F.2d 664 (CCPA 1966), reversed an obviousness rejection where the Examiner had concluded that the claims were merely directed to a crystalline form of an old compound. *See id.* at 666.

Although the examiner in *Cofer* had reasoned that similar compounds were disclosed as having been crystallized in the prior art (*see id.*), the court found that "the record fail[ed] to support a holding that those skilled in the art should have known that [the prior art compound] would exist in crystalline form or that it would be known how to obtain such crystals. We think it improper to presume such knowledge under the circumstances." *Id.* at 668.

The court reasoned:

> To be sure, whether a given chemical compound or composition has the same usefulness as closely related materials may be an important consideration in determining obviousness under 35 U.S.C. § 103. But it is only one consideration. We think the board failed to address itself to other factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form. The new form of the compound set forth in the claims is as much a part of the 'subject matter as a whole' to be compared with the prior are as are other properties of the material which make it useful.

Id. at 667-668.

As Appellants point out, the court in *In re Hoeksema*, 399 F.2d at 274 similarly held that "the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds."

Lastly, as stated in *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . . After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

Id. at 1445.

ANALYSIS

Based on a preponderance of the evidence, we agree with Appellants that the Examiner did not make out a prima facie case of obviousness with respect to either reference.

In contrast to the situation in *Pfizer v. Apotex*, in the instant case Teicher differs from the claims not only in the reference's failure to explicitly disclose the claimed monohydrochloride salt form, but also in its failure to disclose the specific crystalline form claimed. In our view, the Examiner has not adequately explained, through evidence or sound scientific reasoning, why Teicher's teachings would have led an ordinary artisan to the precise crystalline salt form recited in claim 2.

We agree with the Examiner that Teicher discloses that the compound recited in claim 2 can exist in salt forms, including hydrochloride salts (FF 9). We also note Teicher's disclosure of using the dihydrochloride salts in the examples (FF 11). We further note Teicher's disclosure of solvates prepared from crystallization of the salts, using solvents including methanol (FF 10), a solvent disclosed in Appellants' Specification as being useful for preparing the crystalline form of the monohydrochloride salt recited in claim 2 (FF 5).

However, the Examiner has not pointed to any specific teaching in Teicher, or anything in the knowledge of an ordinary artisan, that would have allowed or prompted an ordinary artisan to move from Teicher's generic teaching of the suitability of crystallizing salts, to the *specific* crystalline form of the *specific* salt recited in the claims. Nor has the Examiner explained why an ordinary artisan would have considered it obvious that the crystalline form of the monohydrochloride salt would exist.

The Examiner urges, rather, that Appellants have failed to show that the claimed monohydrochloride crystalline salt is different than Teicher's dihydrochloride salt (Ans. 7-8).

We are not persuaded by this argument. As noted above, the Specification provides evidence that the mono- and dihydrochloride salts are distinguishable (FF 3-7).

Moreover, it is the Examiner who bears the burden of making a prima facie case that a claim is unpatentable. *In re Oetiker*, 977 F.2d at 1445. In the instant case the Examiner has not adequately explained *why* the teachings of Teicher would have taught or suggested to a person of ordinary skill in the art the *specific* crystalline form of the *specific* monohydrochloride salt recited in claim 2.

Thus, we do not agree that the potential existence in the prior art of crystals of the dihydrochloride salt, by itself, and without more, renders obvious the specific monohydrochloride crystals, having the specific X-ray diffraction pattern, recited in the claims. Accordingly, we reverse the Examiner's obviousness rejection of claims 2 and 15 over Teicher.

Heath's disclosure is much less specific regarding the particular salts prepared, mentioning neither monohydrochloride nor dihydrochloride. Moreover, the compound recited in claim 2 is only one of a number of other compounds prepared in that reference.

As the Examiner's rejection suffers from at least the same shortcomings seen with respect to Teicher, we also reverse the Examiner's obviousness rejection of claims 2 and 15 over Heath.

SUMMARY

We reverse the Examiner's obviousness rejection of claims 2 and 15 over Teicher.

We also reverse the Examiner's obviousness rejection of claims 2 and 15 over Heath.

REVERSED

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